REMARKS

I. Status of the Claims

Claims 1-2 are currently pending. Claims 1-2 have been amended to correct typographical errors. No new matter has been added by way of these amendments.

II. Rejections under 35 U.S.C. § 103

A. Assateerawatt in View of Donnelly

The Examiner has maintained the rejection of claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Assateerawatt et al. (*Asian Pac. J. Allergy Immunol.*, 11:85-91, 1993 (IDS)) in view of Donnelly et al. (*J. Immunol. Methods*, 176:145-152, 1994 (IDS)). Applicants respectfully traverse this rejection.

Claim 1 recites "[a] method for immunizing an infant human against a target antigen, comprising inoculating the infant human with . . . a naked recombinant nucleic acid . . . within the age of birth to one month."

1. Assateerawatt

As conceded by the Examiner, Assateerawatt does not teach a method of immunizing an infant human comprising inoculating the infant human with a naked nucleic acid within the age of birth to one month.

As disclosed in the specification, "[t]he concept of tolerance is associated with the traditional belief that neonates are themselves incapable of mounting an effective immune response," and "[i]t has been generally believed that neonates rely on maternal antibodies (passively transferred via the placenta) for immunity, until the neonate begins to synthesize its own IgG anti-bodies (at about 3-4 months after birth, in humans)" (page 3, lines 1-5 (citation omitted)).

As reported in Assateerawatt, newborns in group A received HIBG at birth plus a recombinant protein vaccine, GenHevac B Pasteur, at birth 1, 2 and 12 months of age while newborns in group B received only GenHevac B Pasteur (abstract, p. 86), and the immunogenicity of the vaccine was evaluated by determining the seroconversion rate in these newborns at months 2, 4, 12, 13 and 24 (abstract, pp. 87-88, Figure 1, Table 2). At month 2, newborns exhibited seroconversion rates of 61.9% for group B and 100% for Group A, which were significantly different (Table 2). Starting at month 4, seroconversion rates for groups A

and B were very high and exhibited no significant difference (p. 87; Table 2). The experimental design and results reported in Assateerawatt are consistent with the then conventional view of infant tolerance and the general knowledge that human neonates start to synthesize their own antibodies at about 3-4 months after birth.

Assateerawatt does not teach whether and/or to what extent an epitope encoded by a nucleic acid would be expressed and capable of inducing immune responses in an infant human after being inoculated with the naked nucleic acid within the age of birth to one month. One of ordinary skill in the art would have expected a lower amount of the expressed epitope in such an infant human than that in an infant human injected with the epitope. In view of the significantly lower seroconversion rate in newborns who received a protein vaccine alone than that in newborns who received the protein vaccine plus HIBG at birth, one of ordinary skill in the art would have expected an even lower seroconversion rate in newborns inoculated with a naked nucleic acid encoding the protein. Thus, one of ordinary skill in the art would not have been motivated to modify the protein vaccination method disclosed in Assateerawatt by inoculating an infant human with a naked nucleic acid within the age of birth to one month with a reasonable expectation of success in inducing immune responses in the infant human.

Prior to the present invention, "[i]t was unknown, however, that such [nucleic acid] vaccines could be used to induce an immune response in infant mammals." Specification, page 4, lines 12-13. The instant application describes that inoculation of an infant nonhuman mammal (*e.g.*, newborn baboons and mice) with a naked nucleic acid encoding a relevant epitope of a target antigen induced immune responses in the infant mammal in Examples 6-9. Based on the immune responses induced in newborn nonhuman mammals such as baboons and mice inoculated with naked nucleic acids described in the instant Application, one of ordinary skill in the art would have expected induction of immune responses in an infant human similarly inoculated with a naked nucleic acid within the age of birth to one month.

2. Donnelly

Donnelly does not teach a method of immunizing an infant human comprising inoculating the infant human with a naked nucleic acid within the age of birth to one month.

The Examiner contends that "Donnelly discusses methods for inducing immune responses with DNA including hepatitis B virus surface antigen (HBsAg) (p 147, 2nd column last p[a]ragraph bridg[ing] to p 148)." In fact, Donnelly states that "Benvenisty and Reshef

(1986) obtained expression of . . . hepatitis B surface antigen (HBsAg) by intraperitoneal injection of calcium phosphate-precipitated DNA" (p. 147, 2nd column last paragraph bridging to p. 148). Benvenisty and Reshef (*PNAS* 1986;83:9551-55; "Benvenisty;" attached as Ex. A) discloses that injection of plasmid DNA encoding HBsAg intraperitoneally into one-day-old rats resulted in the expression of HBsAg in liver after 48 hours (abstract, p. 9553; Fig. 4). Benvenisty also teaches that "the hepatitis B virus is incapable of infecting this animal species" (p. 9553, 2nd column), and does not disclose any immune responses in the rats. One of ordinary skill in the art would not have expected any immune responses induced in the rats inoculated with the plasmid DNA, and any correlation of the expression of HBsAg with any immune responses in the inoculated rats. Accordingly, one of ordinary skill in the art would not have been motivated by Benvenisty or Donnelly to inoculate an infant human with a naked nucleic acid encoding HBsAg within the age of birth to one month with a reasonable expectation of success in inducing immune responses against HBsAg in the infant human.

3. Combination of Assateerawatt and Donnelly

A combination of Assateerawatt and Donnelly does not teach each and every element of claim 1. Neither reference teaches a method of immunizing an infant human comprising inoculating the infant human with a naked nucleic acid within the age of birth to one month. It was unpredictable whether and/or to what extent an epitope encoded by a nucleic acid would be expressed and capable of inducing immune responses in an infant human after being inoculated with the naked nucleic acid within the age of birth to one month.

Furthermore, although Donnelly states that "[i]mmunization with DNA is a simple, robust, and effective means of eliciting both antibody and cell-mediated immune response," it also states that "[t]he therapeutic uses of DNA vaccines are beginning to be explored," and "[t]he extent to which this method [of immunization with DNA] can be applied to proteins not of vertebrate origin, e.g., antigens from bacteria and protozoan parasites, remains to be determined" (p. 150).

For the foregoing reasons, one skilled in the art would not have been motivated to combine Assateerawatt with Donnelly with a reasonable expectation of success in achieving the claimed invention of claim 1. Thus, the Examiner has not established a *prima facie* case of obviousness. Applicants respectfully request withdrawal of this obviousness rejection.

B. Assateerawatt in View of Donnelly and Further in View of Chisari

The Examiner has also maintained the rejection of claims 1-2 under 35 U.S.C. § 103(a) as being unpatentable over Assateerawatt in view of Donnelly and further in view of Chisari et al. (*Springer Semin Immunopathol*, 17:261-282, 1995). Applicants traverse this rejection.

For the reasons set forth above, Assateerawatt and Donnelly do not teach a method of immunizing an infant human comprising inoculating the infant human with a naked nucleic acid within the age of birth to one month, and one of ordinary skill in the art would not have been motivated to combine Assateerawatt with Donnelly with a reasonable expectation of success in achieving the claimed invention of claim 1 or 2.

The Examiner cites Chisari to make up the deficiency of Assateerawatt and Donnelly for not teaching "an inclusion of more than one relevant epitope of one or more antigens associated with the pathogen." It is noted that claim 1 does not recite "more than one relevant epitopes of one or more antigens." More importantly, Chisari does not cure the deficiencies of Assateerawatt and Donnelly as set forth above.

Thus, the Examiner has not established a *prima facie* case of obviousness of claims 1 and 2 over Assateerawatt, Donnelly and Chisari. Applicants respectfully request withdrawal of this obviousness rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Withdrawal of all rejections is also requested.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or refund any overpayments to Deposit Account No. 02-4377.

Respectfully submitted,

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